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EXAMINER	
CAPUTA, A	
ART UNIT	**PAPER NUMBER**
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DATE MAILED: 11/29/94

This is e communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 9/24/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☒ See Interview Summary Paper No. 23

Part II SUMMARY OF ACTION

1. ☒ Claims 1-3, 10-16 are pending in the application.
   Of the above, claims 4, 5 are withdrawn from consideration.
2. ☒ Claims 6-9, 17-20 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-3, 10-16 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

1. Applicants' Amendment (Paper No. 20), Declaration (Paper No. 21) and Disclaimer (Paper No. 22) was entered 9/29/94. Claims 6-9, and 17-20 are cancelled. Claims 4-6 are withdrawn from consideration as set forth in Paper No. 14. (Note: From Applicants' Statement (see Paper No. 20-page 22)) it appears that applicants intend to cancel those peptide not from Ro/SSA. However from applicants' amendment it appears that applicants inadvertently did not cancel claims 4 and 5).

2. The finality of the rejection of the last Office action is withdrawn.

3. The elected species as elected by applicant is free of prior art. An examination of species No. 27 as set forth on Paper No. 9 mailed 08/09/93 is be examined for prior art.

4. The prior objection to the use of trademarks is maintained since they should be capitalized (i.e TWEEN) wherever they appear and be accompanied by the generic terminology.

Applicants assert there is no requirement that the trademarks be in capital letters nor generic terminology be used in all cases if not known. Applicants arguments are not persuasive. If the product cannot be otherwise defined, an amendment defining the process of its manufacture may be permitted. Such amendment must be supported by satisfactory showings establishing that the specific nature or process of manufacture of the product as set forth the amendment was known at the time of filing of the application. See MPEP 608.01 (v).

5. The prior objection to the title of the invention is maintained. Applicants' amendment is noted. However since the claimed title is not amended to peptides of Ro/SSA which reflect the claimed invention the objection is maintained.

6. The prior provisionally rejection of claims 1-3 and 7-20 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11-17, 26, 29, 31, 56, and 64 of copending application Serial No. 07/648,205 is withdrawn.

The terminal disclaimer filed on 9/29/94 (Paper No. 22) disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of Copending Application Serial No. 07/648,205 has been reviewed and is accepted. The terminal disclaimer has been recorded.

7. The prior rejection of claims 1-3, and 7-20 under 35 U.S.C. § 112, second paragraph (b) is withdrawn in view of applicants' amendment.

8. The prior rejection of claims 7-9, 17-20 directed to a product and method drawn to therapeutic applications under 35 U.S.C. § 101 is withdrawn since said claims are cancelled.

9. The prior rejection of claims 1-3, and 10-16 directed to a product and method of using the product for diagnostic applications under 35 U.S.C. § 101 is withdrawn in view of applicants arguments.

10. The prior rejection of claims 1-3, and 10-16 under 35 U.S.C. § 112, first paragraph (a), is withdrawn in view of applicants arguments.

11. The prior rejection of claims 7-9, 17-20 under 35 U.S.C. § 112, first paragraph, is withdrawn since said claims are cancelled.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach one of ordinary skill in the art how to make and/or use the claimed invention, i.e. failing to provide an enabling disclosure.

b. The specification provides evidence of octapeptides beginning with the amino acid numbered 308, 313, 315, 481, 484, 489 that are recognized by anti-Ro/SSA greater than A_{410} of 0.3 (see Table 2-page 18), a level in which the peptides did not bind normal sera (see Example 2; pages 16-20). However, the specification provides an insufficient guidance to which region of the octapeptide recognize the antibody (i.e. peptides shorter than 8 amino acids) and peptides of up to 40 amino acids in length that are useful for diagnosis. It would not have been expected that shorter peptides (i.e. 4-7 amino acids in length) would have been useful since: 1.) peptides would not share the same amino acid composition, and therefore the epitope which recognizes the antibody and 2.) peptides which are small in length would not be expected to have the same structure as the octapeptide. Since applicants' have provided no guidance beyond octapeptides which are useful for diagnosis it would have been undue experimentation to determine which portions of the peptides recognize the epitope as broadly claimed.

Additions of amino acids to the peptide would have been expected to alter structure and the recognition (e.g. binding) of

antibody to the antigen due to ionic or covalent binding between amino acids of a peptide. Furthermore the scope of the claims must bear a reasonable coorelation with the scope of enablement. See in re Fischer, 166 USPQ 19 24 (CCPA 1970). As described in the art at the time of the invention it appears that no reactivity was found with hexapeptides of a reactive epitope (see Virji et al. Journal of General Microbiology 135(7):1895-1898; especially page 1898 and Figure 2).

Applicants appear to argue the deletion and substitution of the peptides showing only six amino acids as disclosed in the specification (page 25, 3rd paragraph; page 26; page 28 last paragraph) is sufficient to overcome the rejection. The deletion and substitution studies of octapeptide as disclosed in the specification are not useful for the predicting the outcome of which deletions and substitutions of the elected species are useful since 1.) the octapeptide as disclosed in the specification does not share a similar amino acid sequence and are not from the same protein as the elected species and 2.) the studies were done with only one octapeptide (i.e. PPPGMRPP).

c. The specification provides evidence that sera of patients with a reaction to the 60 kDa protein react with the elected species at greater than a fixed value and less than this value with normal sera. However the specification provides no guidance of the reaction of using different peptides of the elected group to autoantibodies and the prognosis of the patient as newly amended (see claim 16). Applicants amendment to the claimed invention is not sufficient to overcome the rejection. Since the specification provides no guidance: 1. to what different peptides are useful for predicting the prognosis as claimed and 2. what antibodies and level of antibody are related the severity of the disease(s) and it would not have been expected that each peptide would have same specificity, and reactivity it would be unpredictable and an undue burden to

ascertain what peptides if any are useful as a method to predict the prognosis of the patient as claimed.

Applicants argued previously (see Paper No. 17) a higher titer of antibodies correlate with a higher severity of disease. Applicants arguments are not persuasive since applicants have provided no evidence to this correlation. There is no evidence a particular level of antibody is associated with particular symptom and that each patient would present the same clinical signs with an equivalent concentration of antibody. Accordingly, it would it would be an undue burden to ascertain the use of the method to predict the prognosis of the patient as claimed. For the reason stated above and in the last Office Action said rejection is maintained.

d. The specification provides insufficient guidance of using the elected peptides as a method for screening autoimmune diseases as broadly claimed. The specification provides evidence that the peptide recognizes patients with SLE. However, since the specification provides no evidence that elected peptides are capable of screening for other autoimmune diseases as broadly claimed and it would not be expected that other autoimmune diseases respond immunologically in the same manner as SLE, given that each autoimmune disease differ in pathogenesis it would be unpredictable to determine which of the autoimmune diseases the elected species are useful as broadly claimed.

13. The prior rejection of claims 1-3, and 10-16 under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

15. Claims 1-3 and 10-16 are rejected under 35 U.S.C. § 103 as being unpatentable over Deutscher et al. (PNAS 85:9479-9483 December 1988), in further view of Wotiz et al. (U.S. Patent No. 5,312,752; Effective filing date July 1989), Voller et al., and Geysen et al.

Deutscher et al. teach the amino acid sequence and the nucleic acid sequence of the 60 kDa human ribonucleoprotein (see Figure 5). Deutscher et al. teach the recombinant protein is useful for detection of autoantibodies in the sera of patients with autoimmune disorders (see Abstract and Figure 5). Deutscher et al. teach the location of the zinc-binding finger motif is found at amino acids 305-323 (see page 9482; Column 2 and Figure 5). Deutscher et al. teach the zinc finger plays a role in binding of protein to nucleic acid (see page 9483; Column 1). Deutscher et al. does not teach isolating peptides comprising the zinc finger.

Woitz et al. teach that polyclonal antibody to the zinc figure like structure of the human estrogen receptor is specific for the human estrogen receptor and did not cross react with other various steroid receptors (see Column 16, line 55-Column

17-line 28). Woitz et al. teaches that the polyclonal antisera is useful for immunoassays and that it is expected a wide variety of immunoassays may be employed (see Column 7).

It would have been obvious to one of ordinary skill in the art to isolate the peptide comprising the zinc binding motif at amino acids 305-323 as described by Deutscher et al. and use said peptide for diagnosis since as described by Woitz et al. antibodies to zinc figure like structure are specific and useful for diagnosis. It would have been expected to one of ordinary skill in the art a peptide comprising the zinc finger motif as described by Deutscher et al. would have been specific as the zinc finger region as described by Wotiz et al. since said region is characterized by both Deutscher et al. and Woitz et al. as a zinc finger DNA binding region. Furthermore said region as disclosed by both Deutscher et al. and Wotiz et al. both contain histidine and cysteine residues.

Voller et al. teach an indirect method using the ELISA assay to determine the antibody that is found in the sera by immobilizing the antigen on a substrate such as a plate and a sandwich method to determine the antibody by immobilizing the antigen on the plate and an antigen which is enzyme labeled (see pages 99-101).

It would have been further obvious to use a peptide comprising the zinc finger binding motif of the human Ro protein as described by Deutscher et al. in a assay for the detection of antibody as disclosed by Voller et al. since a peptide comprising the zinc finger region as described by Deutscher et al. would have been expected to have be specific in view of the teachings of Wotiz et al. as set forth above.

Geysen et al. teach a method to identify antigenic determinants by testing antibody reactivity against a set of overlapping peptides representing the sequence of the protein.

It would have been further obvious to one of ordinary skill in the art to use the method as described by Geysen et al. to identify the peptides of zinc binding motif at amino acids 305-323 as described by Deutscher et al. in view of Wotiz et al. in the assay for the detection of antibody as disclosed by Voller et al. since the chemical synthesis of smaller peptides derived from a large peptide containing the zinc finger binding motif is more economical to make than the larger peptide.

Thus the claimed invention as a whole is clearly prima facie obvious, especially in the absence of evidence to the contrary.

Parent Application Serial No. 07/648,205 (and 07/472,964) lacks an adequate written description under 35 U.S.C 112, first paragraph of the patentable utility (i.e. diagnosis) for the peptide that begins with 308, 313, 315 as claimed (i.e. that the peptide that begins with 308, 313, 315 is specific for sera from patients and non-reactive with normal patients). Accordingly the filing date for said species is the effective filing date of the instant application.

16. Claims 1-3 and 10-16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 10-16 are rejected since it is not clear as to the minimum length of the recited peptide. Does applicant intend to claim a peptide of a minimum length of 1, 2, 4 or 8 amino acids.

Claims 1-3, 10-16 are rejected for the phrase "sequence of the epitope". It is suggested that applicants said phrase with the "sequence of the peptide'. Furthermore it is unclear as to what amino acids the peptide as claimed contain following the listed amino acid sequence as recited.

Claims 12-16 are rejected since it is unclear what autoimmune disorders applicants intend the method as claimed being used for?

Claim 16 is rejected for the use the term different. It is unclear as to what constitutes as different. Do applicants

intend said claim to encompass a octapeptide which differs from a second octapeptide of one amino acid.

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Barakat et al. teaches of two C-terminal fragments (495-518, and 524-538) had no antigenic activity (see Discussion, 1st paragraph).

Ben-Chetrit et al. teaches of the cDNA sequence of the 60 kDA SSA/Ro protein.

Frank et al. (WO 91/17171) teaches that portions of the Ro/SSA antigen are useful for diagnosis and for treatment.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Anthony C. Caputa, whose telephone number is (703)-308-3995. The examiner can be reached on Monday-Thursday from 8:30 AM-6:00 PM. The examiner can be reached on alternate Fridays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Ms. Christine Nucker, can be reached on (703)-308-4028

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703)-308-0196.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the official Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703)-305-3014 or (703)-308-4227 [Back-up].

Anthony C. Caputa, Ph.D.
November 12, 1994

CHRISTINE M. NUCKER
SUPERVISORY PATENT EXAMINER
GROUP 180